

## PROTOZOA AND CARCINOMA.<sup>1</sup>

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In discussing the question of the cause of cancerous tumours, and specially of the connection existing between parasites and tumours, it is not my intention to review or discuss the work of a large number of observers who have written on the subject during the last fifty years. It was not even my intention to add anything new to what I have already said on this subject last year at the International Congress of Hygiene and Demography.<sup>2</sup> Dr. Ruffer has, however, again brought the question before our mind, and his paper following rapidly on that of Soudakewitch, is not unlikely to make many believe that parasitic protozoa have actually been proved to exist in cancer.

This I think would be a premature conclusion, for the bodies described have not been proved to be parasitic or even to be protozoa. Without forgetting the observations of many who have worked previously in the same field, I will simply confine my remarks to what I have observed myself. In a previous paper<sup>3</sup> I have alluded to the work of a great number of older writers (I was unfortunately unacquainted with the more recent work of Darier, Albarran, and a few others which had just been, or was being, published when I began my researches). I may say that my interest in this question arose perfectly independently of any intention to investigate the etiology of cancer. It was only as a result of my study of psorospermosis as a disease of the rabbit that I was led to consider the possibility of a relation between psorospermosis and epitheliomata. The subject presented itself to me as it seems to have presented itself to the mind of a number of previous observers. From this it will be evident that if I am prejudiced in any way it must be rather in favour of a connection between protozoa and cancer than in favour of the opposite view.

From the beginning it seemed evident to me that in investigating this question one was bound to follow the rules usually followed in bacteriological investigations, for such rules apply to all parasites, whether animal or vegetable. I therefore studied carefully all the forms which could be observed in the rabbit's liver, both with regard to their

<sup>1</sup> This communication was illustrated by photographs and drawings shown by the lantern. Some of them are reproduced here.

<sup>2</sup> BRITISH MEDICAL JOURNAL, 1891, ii, p. 362.

<sup>3</sup> Abstract, BRITISH MEDICAL JOURNAL, 1889, ii, p. 1393; Trans. Path. Soc., xli, 1890.

morphological characters and to their reactions with various reagents. I found, like others before me, that they could be extremely well seen without the help of any special method of preparation. In sections fixed with osmic acid it was easy to recognise a number of forms:

1. A young coccidium or psorosperm looks much like a nucleus with sometimes a large nucleolus (the previous stages are difficult to make out when embedded in a cell).

2. Larger organisms are ovoid in shape and contain a mass of very coarsely granular protoplasm, in which there is a more or less distinct nucleus-like body. Many of the granules stain black with osmic acid, mahogany brown with iodine, pink with fuchsin, and so on.

3. Most of these oviform bodies have a distinct capsule with double outline, and among the encapsulated bodies there are some which stain deeply with fuchsin.

4. Some of the parasites contain one or several long coiled filaments.

5. Very large bodies, two or three times the size of the others, with comparatively small granules sometimes arranged



Fig. 1.—Endogenous cell formation in a secondary squamous epithelioma of a lymphatic gland. The nucleus of the mother cell is partly between the encysted daughter cell and the observer, so that, although flattened, it still looks round.  $\times 1100$ .

in radiating lines, and with a large indistinct nucleus, are found here and there among the other parasites. These various forms have been described and depicted in the paper already alluded to above<sup>4</sup> and in a later communication.

I now looked for similar appearances in epithelial tumours, using the same methods of preparation and keeping in mind the possibility of important differences between the parasite of the rabbits' tumours and the possible one that might be found in human tumours. I have elsewhere<sup>5</sup> shown why (though thinking that the parasitic origin of cancer is, on theoretical grounds, not probable) it is possible to suppose

<sup>4</sup> *Trans. Path. Soc.*, vol. xli, p. 346, Plates XXI, XXII, XXIII.

<sup>5</sup> *Trans. 7th Int. Cong. Hyg. and Dem.*, BRITISH MEDICAL JOURNAL, 1891, ii, p. 362.

that a cellular parasite might act as causal agent, the reason being simply that the parasite might be carried from the primary focus of infection to the various places where secondary tumours occur, in some of the cells entering into the formation of the original tumour. This supposition is, I believe, absolutely necessary to reconcile what we know of the metastasis of epithelial tumours with the idea that they might have a parasitic origin. There was no difficulty in finding in a number of epithelial tumours (squamous, cylindrical, and glandular epitheliomata, that is, carcinomata) bodies very similar to some of the younger and least distinct forms of coccidia, and which might therefore have been young coccidia or allied protozoa. In some cases the appearances were very striking, but side by side with bodies simulating closely parasites, were others having apparently the same relations



Fig. 2.—Liver seen from its lower aspect. The bile ducts and the gall bladder are opened to show the cancerous thickening of their walls. A small portion of the duodenum and a part of the pancreas are also shown twisted out of their normal position to show the openings of the common bile duct and of the pancreatic duct in the duodenum (reversed in the process of reproduction).

to the enclosing cells, and which were distinctly the result of endogenous cell formation in a state of more or less advanced degeneration. In some cases I have been able to see in the enclosed body radiating lines corresponding in arrangement and size to the prickles abundantly seen at the periphery of the cells forming the tumour examined (a squamous epithelioma). The appearances presented by these products of endogenous formation were described by Virchow in 1847 and 1851. Endogenous cell formation in a secondary epithelioma affecting a lymphatic gland is shown in Fig. 1. Though the enclosed body is distinctly a cell it seems enclosed in a capsule, and presses the nucleus of the mother cell to one side just as the suspicious bodies would do.

Many of the enclosed bodies have exactly the appearances described by Darier, Albarran, and others, and also depicted by Wickham, Hutchinson, and Bowlby; others resemble still more closely young stages of coccidia. None of these bodies, however, corresponded exactly in reactions to those found in

the rabbit's liver, nor did they show any unmistakable evidence of division of the contents of one capsule. I thought that these differences might have been due to the nature of the pabulum. In the rabbit's liver the parasites are in bile ducts, containing more or less altered bile, and surrounded by liver cells containing glycogen and other products.

In ordinary carcinomata the surroundings are very different. I therefore searched for a liver presenting lesions analogous to those found in the rabbit's liver. Early in 1890 I found a case of primary carcinoma of bile duct and liver parenchyma (Fig. 2). This liver was obtained from a case under the care of Dr. Dickinson at St. George's Hospital. Dr. Dickinson kindly provided me with the clinical notes and allowed me to make use of the case for this investigation. The patient was a married woman, aged 49, who had had 11 children, and had always enjoyed good health till a few months before her death; eight weeks only before the fatal event jaundice became manifest. At the *post-mortem* exami-



Fig. 3.—An antero-posterior, vertical section of the same liver, photographed from Nature to show the distribution of the cancerous nodules in the liver parenchyma.

nation the liver was found full of nodules, large and small, rather soft, and evidently cancerous (Fig. 3). The common bile duct, the hepatic ducts, and all their branches were found much thickened by a papillomatous-looking epitheliomatous growth. The gall bladder was in the same state, and contained in addition a large number of gall stones; it must be remembered that the patient did not show any evidence of jaundice until eight weeks only before her death, so that the gall stones must have been rather the result than the cause of the state of the gall bladder. On dissecting the organ carefully it was found that all the cancerous nodules were situated either at the end or on the course of bile ducts. No other organ than the liver was affected; there was only a slight extension of the growth along the portal lymphatics to the retroperitoneal glands in the neighbourhood of the foramen of Winslow. The pancreatic duct was not affected at all. I naturally examined carefully the walls and contents of the

bile ducts, and also the cancerous nodules. I examined them fresh, and after hardening and staining them in various ways, and I drew immediately some of the bodies which seemed to

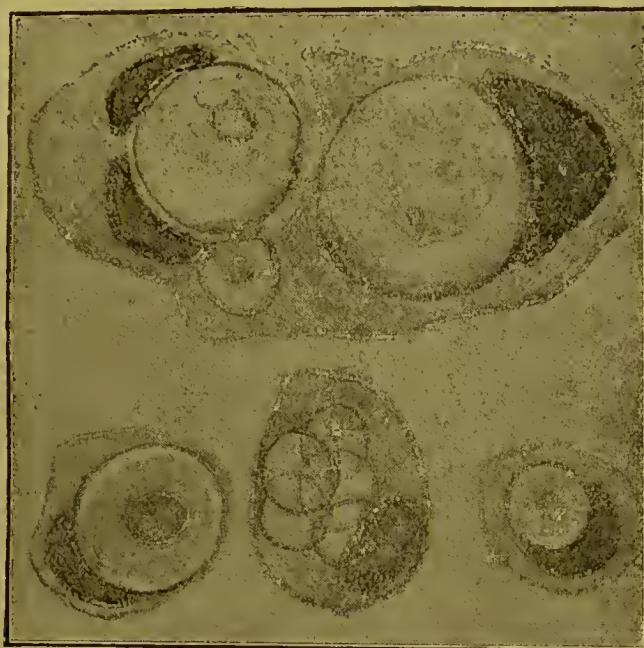


Fig. 4.—Various forms of psorospermoid bodies found in the cells of a primary cancer of the liver.  $\times 1100$ .

me to resemble coccidia, though I could not find any quite identical with those found in the rabbit's liver. What seemed



Fig. 5.—A number of psorospermoid bodies in the midst of a group of cancer cells imperfectly separated from each other.  $\times 1100$ .

to me most conclusive was that some of them showed what appeared to be evidences of multiplication within their

capsule. I thought for a time I had found the right bodies at last, and I even announced at a meeting of the Pathological Society (March, 1890) that I had found psorosperms in that case of carcinoma of the liver. (B.M.J., 1890, i, p. 664.)

I regret not to have had these bodies photographed; but I have taken accurate drawings of them with the camera lucida (Figs. 4 and 5), and I think it would be difficult to doubt the identity of these bodies and of those described by Soudakewitch and Ruffer (and of some of those described by Russell). But even in this case, which presented all the conditions favourable to the development of psorosperms, I was unable to find indubitable proof of the parasitic nature of the suspicious psorospermoid bodies.

I began then to cultivate the coccidia of the rabbit's liver, and soon found that in simple scrapings of a psorospermic nodule kept in a moist chamber at the ordinary temperature, or at a temperature of 20° C., it was possible to observe within



Fig. 6.—Some of the forms observed in psorosperms kept in a moist chamber in some nutrient medium.  $\times 1100$ .

a few days very typical stages of division in the coccidia. I gave an account of these results in May, 1891, at a meeting of the Pathological Society, and demonstrated without any difficulty the changes described and figured in the *Transactions* of the Society (vol. xlvi, Pl. VII). Some of the most typical stages are represented in Fig. 6. I have several times tried to observe similar or analogous changes in psorospermoid bodies contained in scrapings of carcinomata treated in the same way as the scrapings of psorospermic nodules, but as yet I have failed to obtain definite results.

I have now stated my reasons for doubting the parasitic nature of bodies which I myself thought at first were parasitic, and which I have even described as such more than two

years ago. These bodies I have not the slightest doubt, after comparing my specimens with those of Dr. Ruffer and the drawings published by Soudakewitch, are identical with most of the forms described by these observers. I therefore feel justified in asking them to prove the parasitic nature of their bodies.

It is true that they rely on certain typical staining reactions and on certain appearances of multiplication; but I think these criteria are insufficient, for:

A. The staining reactions are unnecessary in such a case, because (1) the bodies are so large and distinct that they can easily be studied with a moderately high power; (2) ordinary methods of staining are quite sufficient, as I have proved; (3) because Dr. Ruffer himself says that these bodies have not always the same reaction, the bodies described and demonstrated by him being extremely variable in that respect; (4) because the same variability of reaction can be observed in products resulting from various protoplasmic degenerations, as may easily be recognised by studying the appearances presented by cells undergoing degeneration, especially the colloid.

B. The evidences of multiplication which are adduced are such that they might easily be produced by endogenous multiplication of cells and nuclei and degenerative changes. I do not say that the bodies in question are not parasites. I only say that certain endogenous productions are much like them, and that no one has proved that these bodies have a life independent of that of the cell. Nobody has shown in them evidences of those stages of development which have been shown to exist in other parasitic protozoa, and are so characteristic in coccidia. I therefore consider that, even with the support of such an eminent authority as Metschnikoff, neither Soudakewitch nor Ruffer has any more right for the present to call the bodies to which they have again attracted attention either protozoa or parasites than those who had described the same or similar bodies previously.

NOTE.—The five concluding paragraphs have been rewritten after the meeting so as to include some remarks made during the discussion, but which are simply explanatory of the text. Figs. 1, 4, and 5 have been prepared specially for this communication from some of my old specimens; they are absolutely accurate. In a previous communication I have had reproduced my older drawings, which being done to the same scale will be comparable. (*Trans. 7th Int. Congress Hyg. and Demography.*) For this communication I have selected those forms only which Soudakewitch and Ruffer have themselves depicted, leaving aside the forms which I consider transitional.



